

## Effect of Caffeic Acid Phenethyl Ester on Wound Healing: A Systematic Review

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### ABSTRAK

Asid kafeik, sebatian organik yang wujud secara semulajadi, mempunyai sifat antioksidan dan anti-radang, bersama dengan bahan terbitannya. Kajian sistematik ini bertujuan untuk menilai kesan asid kafeik dan bahan terbitannya terhadap tekanan oksidatif dan tindak balas keradangan dalam penyembuhan luka kulit. Kajian ini dijalankan mengikut panduan Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Carian dilakukan di PubMed, Scopus, dan Ovid MEDLINE. Artikel yang diterbitkan antara tahun 2000 dan Jun 2022, dengan tujuh artikel yang memenuhi kriteria inklusi telah dipilih. Artikel-artikel tersebut merupakan kajian *in-vivo* yang menggunakan asid kafeik fenetil ester (CAPE) sebagai agen terapeutik dalam tiga jenis luka kulit termasuk kecederaan melecur berketebalan penuh ( $n=4$ ), dua luka insisi dan satu ulser tekanan. CAPE menurunkan kadar spesies oksidatif reaktif dan mengurangkan peroksidasi lipid, superoksida dismutase, nitrotirosin, malondialdehid, katalase, xanthine oksidase, dan paras nitrik oksida. Kawasan luka yang dirawat menunjukkan peningkatan pembentukan tisu granulasi, vaskularisasi, dan kolagenisasi serta kesan jangka panjang CAPE seperti yang dibuktikan oleh pengurangan jumlah miofibroblas, makrofag CD68-positif, dan peningkatan penyerapan kolagen. Kajian sistematik ini menekankan bagaimana kesan antioksidan dan anti-radang CAPE dapat mempercepatkan penyembuhan luka di mana CAPE juga berpotensi besar untuk diaplikasikan dalam penggunaan klinikal.

**Kata kunci:** Antioksidan; asid kafeik fenetil ester; kecederaan haba

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## ABSTRACT

Caffeic acid, a naturally occurring organic compound, possesses antioxidant and anti-inflammatory properties, along with its derivatives. This systematic review aimed to evaluate the effect of caffeic acid and its derivatives on oxidative stress and inflammatory response in cutaneous wound healing. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Searches were performed in PubMed, Scopus, and Ovid MEDLINE. Articles published between 2000 and June 2022, with seven articles meeting the inclusion criteria were retrieved. The articles constituted in-vivo studies that utilised caffeic acid phenethyl ester (CAPE) as the therapeutic agent in three types of cutaneous wound including full-thickness burn injury (n=4), two incisional wounds, and one pressure ulcer. CAPE scavenged reactive oxidative species and reduced lipid peroxidation, superoxide dismutase, nitrotyrosine, malondialdehyde, catalase, xanthine oxidase, and nitric oxide levels. The treated injured area revealed enhanced granulation tissue formation, vascularisation, and collagenisation as well as long-term effects of CAPE as evidenced by reduced myofibroblast amount, CD68-positive macrophages, and increased collagen deposition. The systematic review emphasised how antioxidant and anti-inflammatory effects of CAPE could improve the process of wound healing, suggesting its substantial potential for clinical applications in this domain.

Keywords: Antioxidant; caffeic acid phenethyl ester; thermal injuries

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## INTRODUCTION

A wound is defined as damage or disruption in normal anatomical structure and function. Wound healing involves a number of processes, including haemostasis, acute inflammation, proliferation, and remodelling (Zulkefli et al. 2023). Inflammatory cell infiltration at the local wound site causes the release of lysosomal enzymes and reactive oxygen species (ROS), leading to local inflammatory response as well as clearance of necrotic cell debris (Deng et al. 2021). However, research shows that extensive inflammatory processes,

characterised by abundant neutrophil infiltration may delay the healing process (Zhao et al. 2016). ROS are produced in response to cutaneous injury and may cause cellular damage by peroxidation of membrane lipids, inactivation of sulfhydryl enzymes, cross-linking of proteins and breakdown of DNA (Siti et al. 2015). Research shows that wounding depletes ROS scavengers, which may or may not recover after completion of healing (Wang et al. 2023). The main approach to manage wound healing is through pharmacotherapy intervention. However, pharmacotherapy carries certain risks and adverse effects to the

patients (Semis et al. 2021). Hence, more studies are being conducted to investigate the role of natural products such as caffeic acid phenethyl ester (CAPE), a derivative of caffeic acid, for wound healing with minimal side effects (Dos Santos & Monte-Alto-Costa 2013; Muhammad Abdul Kadar et al. 2021; Romana-Souza et al. 2018).

CAPE, an active constituent found within honeybee propolis extracts, has been harnessed in traditional medicinal practices for the treatment of various maladies (Choudhary et al. 2023). This compound offers a spectrum of advantageous attributes, notably encompassing antioxidative, anti-inflammatory, immunomodulatory, and wound healing properties, as substantiated in extant literature (Muhammad Abdul Kadar et al. 2021; Tolba et al. 2013). An array of investigations has undertaken the examination of the efficacy of CAPE in the management of distinct medical conditions, ranging from cutaneous wound healing and ischaemic-reperfusion injury (Teke et al. 2013), secondary peritonitis (Teke et al. 2012) to cancer (Firat et al. 2019). It is conjectured that CAPE may augment the process of wound healing, as postulated by Armutcu et al. (2004). Therefore, the present study has been undertaken with the objective of conducting a systematic review of pertinent literature concerning the impact of caffeic acid on wound healing, principally attributed to its antioxidative and anti-inflammatory attributes.

## MATERIALS AND METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). This systematic review aimed to evaluate the effect of caffeic acid and its derivatives on oxidative stress and inflammatory response in cutaneous wound healing.

### Search Strategy and Sources

Articles were identified following searches in three electronic databases, which included PUBMED, Ovid Medline and Scopus. Keyword combinations used were (“caffeic acid” OR “caffeic acid derivative\*” OR “caffeic acid ester\*”) AND (“wound\*” OR “wound healing” OR “regeneration” OR “epithelization” OR “ulcer” OR “burn”) AND (“inflammation” OR “oxidative stress”). The articles published between 2000 and June 2022 were extracted.

### Study Selection and Data Extraction

Articles extracted from the databases were imported into Mendeley and duplicates were removed. All electronic search titles, selected abstracts, and full-text articles were independently reviewed by a minimum of two reviewers (W.Z.K., D.S., M.F.H., N.A.A., S.A.S.S.). Disagreements on study inclusion/exclusion were resolved with the consultation of a senior third reviewer. The following inclusion criteria were applied: peer reviewed, English written, and any

types of wounds, published between 2000 to June 2022. In vitro studies, ex vivo studies, review articles, case reports, retrospective investigations, abstracts, studies of mixtures of substances and out of scope study design were excluded in the study. The data collection method of the study was presented in the flowchart in Figure 1. Data was extracted using standardised forms. Extracted information included data regarding authors, year of publication, animal models, total number of animals, wound types, dosages and duration, treatment group interventions, control group interventions and results.

### Quality Assessment

Quality assessment of each study was conducted using Systematic Review Centre for Laboratory animal Experimentation’s risk of bias tool (SYRCLE’s RoB tool) for animal studies, which is an adapted version of Cochrane Risk of Bias (ROB) tool (Hooijmans et al. 2014). In the present study, 10 entries comprised of 11 signaling questions, were used to assess the risk of bias of each individual animal study. The questions were judged by two independent investigators, based on ‘Yes’ which indicated low risk of bias; ‘No’ which indicated high risk of

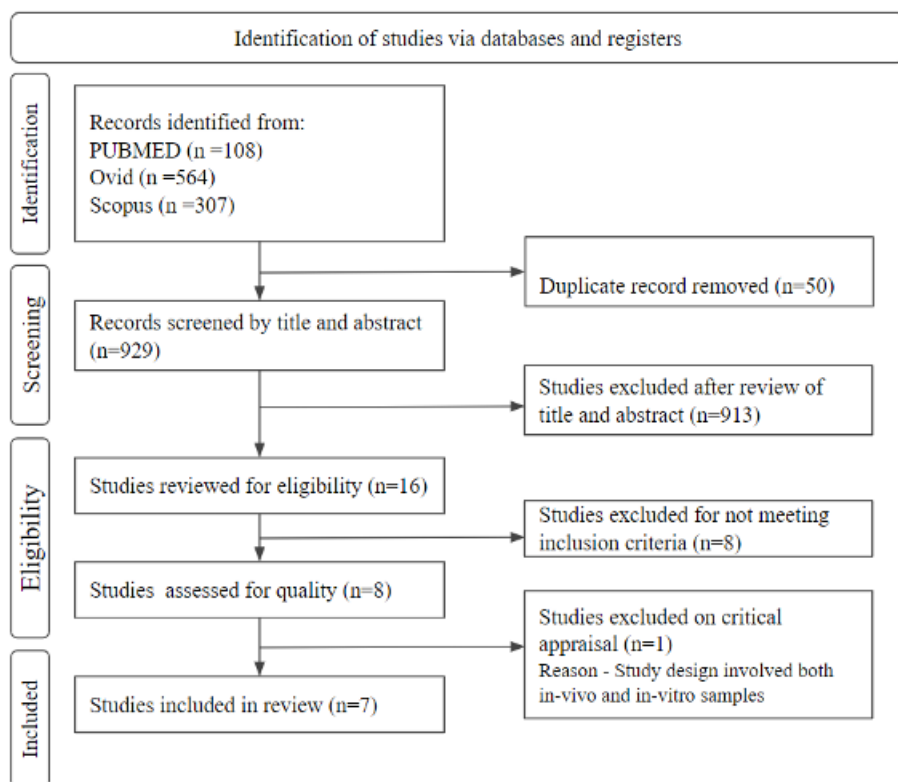


FIGURE 1: Flowchart of studies selection

bias; or 'Unclear' if insufficient details had been reported. These entries were related to six types of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. A summary of the quality assessment (Figure 2) was reported as low risk, high risk or unknown risk of bias with regard to each type of bias.

## RESULTS

In this systematic review, a total of seven papers were examined, all of which lent support to the proposition that CAPE effectively promoted wound healing by harnessing its antioxidant and anti-inflammatory attributes. Notably, all the studies encompassed in this review exclusively employed rodent models, thereby ensuring a high degree of study design uniformity. These animal models for cutaneous wound assessment consisted of four burn wounds, two cases of incisional wounds, and one occurrence of a pressure ulcer. The administration of CAPE was consistently accomplished

through intraperitoneal delivery, with the specific dosage ranging between 5-10 mol/kg, tailored to the unique experimental designs of each study. Detailed information regarding the key characteristics of the studies under evaluation, along with the outcomes of CAPE application in diverse categories of cutaneous wounds, was readily accessible within Table 1.

## Burns

In third degree burn injuries, CAPE exhibited medicinal benefits through its antioxidant, immunomodulatory and anti-inflammatory effects. At the burnt area, CAPE enhanced the reepithelisation and wound contraction, promoted granulation tissue formation and collagen deposition. Additionally, the area revealed decreased myeloperoxidase activity, implying a reduced infiltration of polymorphonuclear cells. Likewise, a similar trend was noticed in the expression of myofibroblasts, platelet endothelial cell adhesion molecule-1

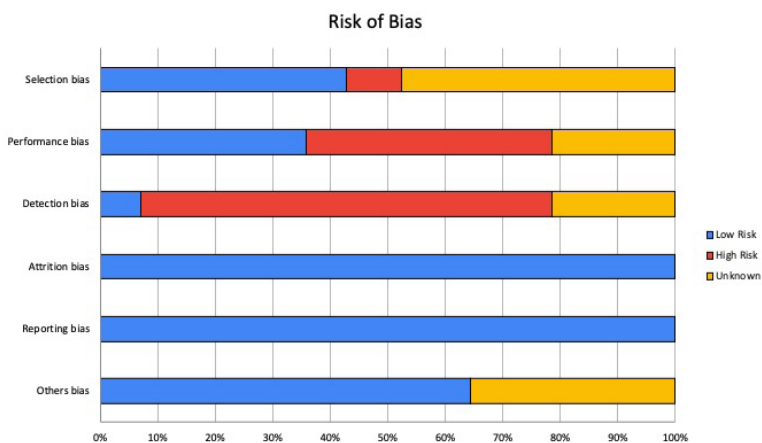


FIGURE 2: Summary of quality assessment

TABLE 1: Studies evaluating the effectiveness of CAPE on cutaneous wound healing

Author, year	Animal model	Total (n)	Wound type	Dosage and duration	Treatment group intervention	Control group intervention	Results obtained
Armutcu et al. (2004)	Male Wistar albino rats	42	Full thickness third degree burn injury (30% of the total body surface area)	10 µmol/kg of CAPE for 7 days	Intraperitoneal injection of CAPE	No treatment	<ul style="list-style-type: none"> <li>-&gt; Thiobarbituric acid reactive substance level</li> <li>-&gt; NO level</li> <li>-&gt; SOD activity</li> <li>-&gt; XO activity</li> <li>-&gt; CAT activity</li> </ul>
Gurel et al. (2004)	Male wistar albino rat	41	Full thickness burn injury (25-30% total body surface area)	10 µmol/kg for 7days	Intraperitoneal injection of CAPE	No treatment	<ul style="list-style-type: none"> <li>-&gt; MDA levels</li> <li>-&gt; myeloperoxidase activity</li> <li>-&gt; XO activity</li> <li>-&gt; SOD and CAT activities then normalised</li> </ul>
Hoşnüter et al. (2004)	Male Wistar albino rats	51	Full thickness burn injury (20% of total body surface area)	10 µmol/kg of CAPE for 14 days	Intraperitoneal injection of CAPE	Serum physiologic	<ul style="list-style-type: none"> <li>-&gt; MDA level</li> <li>-&gt; NO level</li> <li>-&gt; XO activity</li> <li>-&gt; SOD activity</li> </ul>
Dos Santos & Monte-Alto-Costa (2013)	Female Wistar rats	28	Third degree burn injury	10 µmol/kg of CAPE for 14 days	Intraperitoneal injection of CAPE	No treatment	<ul style="list-style-type: none"> <li>-&gt; NO level</li> <li>-&gt; MDA level in plasma and tissue</li> <li>-&gt; Carbonyl levels in plasma and tissue proteins</li> <li>-&gt; Myeloperoxidase activity</li> <li>-&gt; CD68 and PECAM-1 expression</li> <li>-&gt; a-smooth muscle actin expression (volume density of myofibroblast)</li> <li>-&gt; CD68-positive macrophage</li> <li>-&gt; Hydroxyproline levels (increased collagen deposition)</li> <li>-&gt; Granulation tissue formation and rate of wound contraction</li> </ul>

Serarslan et al. (2007)	Male Wistar Albino rats	40	80mm linear full thickness incisional wound	10 µmol/kg of CAPE once a day for 14 days	Intraperitoneal injection of CAPE	No treatment	<ul style="list-style-type: none"> <li>- ↑ GSH level</li> <li>- ↑ NO levels</li> <li>- ↓ MDA level</li> <li>- ↓ SOD activity</li> </ul> <p>Histopathological findings:</p> <ul style="list-style-type: none"> <li>- Day 1, mild fibroblastic activity and vascularisation.</li> <li>- Day 3, increased fibroblastic activity and vascularisation with complete epithelialisation.</li> <li>- Day 7, marked increase in fibroblastic activity and collagenisation.</li> <li>- Day 14, cellular connective tissue and intact epidermis.</li> </ul>
Kontas-Askar et al. (2009)	Male wistar albino rat	40	8 cm linear full thickness incisional wound	25 µmol ml <sup>-1</sup> for 14 days	CAPE	No treatment	<ul style="list-style-type: none"> <li>- ↓ TSA level of serum, wound and liver tissue</li> <li>- ↓ LBSA concentration</li> <li>- ↓ serum TAC level but ↑ wound tissue TAC level</li> </ul>
Romana-Souza et al. (2018)	Male Swiss mice	78	Pressure ulcer	5 µmol/kg of CAPE daily for 12 days	Intraperitoneal injection of CAPE	No treatment	<ul style="list-style-type: none"> <li>- ↑ Nitrite, NOS-2, NF-kB, TNF-α, F4/80-positive macrophage, neutrophil proelastase, nitrotyrosine and MDA level 3 days but 7 days later</li> <li>- ↓ NRF-2 3 days after ulceration but ↑ 7 days later</li> <li>- ↑ Myofibroblast density 7 days after ulceration but ↓ 12 days later</li> <li>- ↑ Re-epithelialised wound area 12 days after ulceration</li> <li>- ↑ Collagen type I and III after 3 days</li> </ul>

CAPE: caffeic acid phenethyl ester; CAT: catalase; GSH: glutathione; LBSA: lipid bone sialic acid; MDA: malondialdehyde; NK-kB: nuclear factor kappa B; NO: nitric oxide; NOS-2: nitric oxide synthase 2; NRF-2: nuclear factor-erythroid2-related factor 2; PECAM-1: platelet endothelial adhesion molecule-1; SOD: superoxide dismutase; TAC: total antioxidant capacity; TNF-α: tumor necrosis factor alpha; TSA: total sialic acid; XO: xanthine oxidase

(PECAM-1) and CD68-positive macrophages (Dos Santos & Monte-Alto-Costa 2013).

Evaluating the effect of CAPE on erythrocyte lipid peroxidation in a rat model of burn injury, CAPE administration hindered both activity of thermal-induced xanthine oxidase (XO) activity and nitric oxide (NO) level, alongside exhibiting an anti-lipoperoxidative capacity. Thus, the benefits of CAPE on the red blood cells may act through its antioxidant, anti-inflammatory and immunomodulatory effects (Armutcu et al. 2004).

At plasma level, CAPE demonstrated the antioxidants activity against free oxygen radicals by saving superoxide dismutase (SOD) activity, preventing XO activity and decreasing the levels of malondialdehyde (MDA), and NO (Hoşnüter et al. 2004).

Systemic oxidant changes from thermal injury may prompt neutrophil and macrophage infiltration in distant organs (Parihar et al. 2008). Furthermore, the protective effects of CAPE against oxidative damage were also investigated on lung and kidney tissues. Treatment with CAPE was profoundly elevated the reduced activities of SOD and catalase (CAT) to the normal level, concurrently diminishing MDA levels, myeloperoxidase and XO activity (Gurel et al. 2004).

### **Incisional Wound**

In full thickness incisional wound, the injured area that subjected to CAPE treatment displayed marked increase in glutathione and NO levels, coupled

with a decline in MDA and SOD levels. Initially, the wound exhibited increased fibroblastic activity and vascularisation, eventually culminating in complete reepithelisation by day three. Intact epidermis with cellular connective tissue was observed at day 14 (Serarslan et al. 2007).

Moreover, significant decreases in serum, wound, and liver tissue Total Sialic Acid, along with serum Lipid Bond Sialic Acid level, were observed in the CAPE group. Furthermore, in comparison to the CAPE group, the control group exhibited a significant decrease in serum and wound tissue Total Antioxidant Capacity levels (Kontas-Askar et al. 2009).

### **Pressure Ulcer**

Ischemia and reperfusion in pressure ulcers prompted the production of ROS leading to prolonged inflammation and tissue impairment, resulting in delayed healing (Reid et al. 2004). In animal model of pressure ulcer, CAPE enhanced the reepithelisation and wound closure at day 12, alongside promoting collagen deposition. Three days post-ulceration, CAPE elevated lipid peroxidation, NO synthesis, macrophage migration, together with an increase in protein nuclear factor kappa B (NF-KB) and nitric oxide synthase-2 expression. However, these factors were observed to decrease seven days later. The opposite pattern was observed in the protein expression of nuclear factor-erythroid2-related factor 2. Myofibroblast demonstrated the similar trend except a decrease was observed 12 days after ulceration



(Romana-Souza et al. 2018).

## DISCUSSION

CAPE was initially detected as a constituent of propolis in 1987 (Bankova et al. 1986). Propolis serves as the primary source of CAPE. CAPE can be acquired from propolis through different extraction techniques or synthesised via various methods, including response surface methodology, starting from caffeic acid and phenethyl alcohols. This process yields molar conversion rates of 96% (Chen et al. 2011) and 91.2% (Chen et al. 2010). CAPE, a natural polyphenolic substance, is known for its anti-inflammatory and antioxidants benefits in various diseases and disorders including metabolic syndrome (Muhammad Abdul Kadar et al. 2021), peritonitis (Teke et al. 2012), diabetic wound (Deng et al. 2021), myocardiac ischemia reperfusion injury (Li et al. 2018) and CNS disorders (Balaha et al. 2021).

The cell houses the antioxidant scavenger system, comprising SOD and CAT. This system works to shield cells from harm caused by superoxide ions produced during inflammatory responses, reperfusion, or burns. SOD plays a crucial function in combating oxidative stress by transforming the superoxide anion into the less biologically active hydrogen peroxide ( $H_2O_2$ ) and oxygen ( $O_2$ ) molecules (Fukai & Ushio-Fukai 2011). Findings on SOD levels yielded conflicting results, with two papers supporting an increase in levels (Gurel et al. 2004; Hoşnuter et al. 2004) and another two

indicating the opposite trend (Armutcu et al. 2004; Serarslan et al. 2007). Initially, SOD level in third degree burn was reduced then followed by an increase to the normal level. The initial decrease may be related to the utilisation of activated enzymes combating oxidative stress. Treatment with CAPE led to an enhancement in enzyme activities (Gurel et al. 2004). This result was consistent with another study which demonstrated increased SOD level after burn injury (Saitoh et al. 2001). Conversely, there is finding showing CAPE hinders the utilisation of SOD, leading to a reduction in lipid damage, ultimately resulting in decreased SOD levels (Armutcu et al. 2004; Serarslan et al. 2007).

CAPE significantly reduced CAT levels parallel to a decrease in lipid peroxidation (Armutcu et al. 2004). Moreover, CAPE enhanced CAT activity, counteracting the oxidative scavenging activity (Gurel et al. 2004). In incision wound, CAT activity remained constant throughout the wound-healing period, suggesting its role in developing resistance against oxidative stress. Additionally, CAT was observed to respond with a delay to an excessive amount of reactive oxygen species (ROS) in comparison to other antioxidants (Serarslan et al. 2007).

NO level was also found to progressively increase in CAPE-treated group throughout the study period (Serarslan et al. 2007). Although NO is produced in oxidative stress, but low level of oxidative stress is beneficial for wound healing (Dunnill et al. 2017). The increase in NO level might be due to the capability of CAPE to increase

NO synthase activity, or prevent consumption of NO by ROS to form peroxynitrite (Förstermann et al. 2017).

MDA is a byproduct resulting from the peroxidation of polyunsaturated fatty acids. MDA has been employed as a biomarker for evaluating oxidative stress in diverse biological samples of a variety of diseases (Cordiano et al. 2023). CAPE significantly decreased MDA levels in burn and incisional wounds, in both plasma and tissue samples (Dos Santos & Monte-Alto-Costa 2013). The anti-lipoperoxidative benefit of CAPE is attributed to its direct function as a scavenger of free radicals (Gurel et al. 2004). Additionally, CAPE is capable of eliminating hydrogen peroxide (Hoşnuter et al. 2004).

During the process of inflammation, XO catalyses the conversion of hypoxanthine to xanthine and then, to uric acid, generating various ROS such as superoxide radical anions and hydrogen peroxide. ROS increases oxidative stress which will lead to further tissue damage (Bhattacharyya et al. 2014). With the knowledge of xanthine oxidase-induced inflammation, inhibition of xanthine oxidase had a significant effect in reducing inflammation. This is consistent with another study that demonstrated the use of allopurinol, a xanthine oxidase inhibitor inhibited superoxide production and decreased oxidative stress in human type 1 diabetes (Desco et al. 2002). In our study, three papers (Armutcu et al. 2004; Gurel et al. 2004; Hoşnuter et al. 2004) had shown that XO activity was lower in CAPE-treated group than the control group. This is attributable to

the anti-oxidative properties of CAPE, which acts on XO enzyme, preventing further tissue damage caused by ROS production.

In term of inflammatory response, reduced ROS production triggered the activation of nuclear factor kappa B nuclear (NF-KB), leading to diminished inflammation, concurrently with the suppression of tumor necrosis factor alpha (TNF- $\alpha$ ) and NO levels (Romana-Souza et al. 2018). Also, CAPE suppressed TNF- $\alpha$ , cyclooxygenase-2 (COX-2), and nitric oxide synthase 2 (NOS2) gene expression, together with NF-KB nuclear translocation (Romana-Souza et al. 2018). CD68-positive macrophages level progressively decreased in CAPE-treated group throughout the study period (Dos Santos & Monte-Alto-Costa 2013). The decrease in CD68 expression might be due to the capability of CAPE to reduce prostaglandin and leukotriene synthesis, acting as potent anti-inflammatory agent (Song et al. 2002). Figure 3 summarises the collective role of CAPE as both antiinflammatory and antioxidant agents in cutaneous wound healing.

All the investigations encompassed in this compilation pertained solely to animal subjects, as, to date, no human studies had been identified. In vivo studies serve as an essential prerequisite prior to clinical trials (Sorkin et al. 2020). The potential limitations and formidable challenges in utilising CAPE in clinical trials warrant careful consideration prior to its implementation. Optimisation of preclinical research before initiating clinical trials involves meticulous

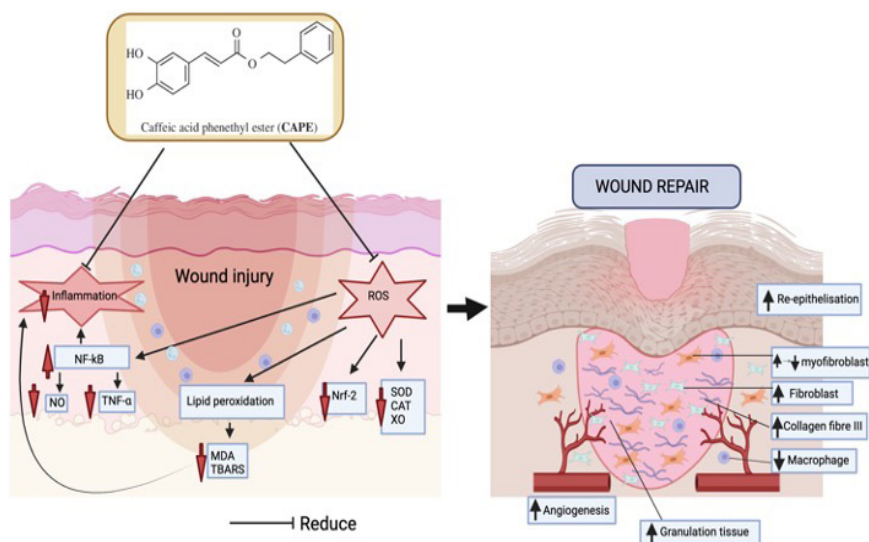


FIGURE 3: This figure summarises the role of CAPE in enhancing cutaneous healing through its antioxidant and anti-inflammatory properties. CAPE scavenged ROS by reducing SOD, CAT, XO levels. Reduction in ROS production also activated NF-kB resulting in reduced inflammation, together with inhibition of TNF- $\alpha$  and NO levels. Microscopically, CAPE stimulated the process of angiogenesis and the development of granulation tissue, thereby contributing to an improved re-epithelialisation process. Initially, myofibroblast population exhibited an initial increase followed by a subsequent decrease. Fibroblast and collagen fiber III levels increased, in contrast to the macrophage response pattern

planning encompassing study design, selection of appropriate animal models, as well as considering the intended dosage and drug delivery system.

A notable methodological limitation observed in all the presented studies is the absence of a positive control group. None of the articles included a positive control group that utilised current treatments for wound healing. This omission restricted the ability to thoroughly assess the therapeutic effectiveness of CAPE in wound healing compared to standard treatment.

Different doses were chosen as the treatment regime. This variation in treatment may account for the difference in treatment outcome.

Doses utilised in studies should be comparable to intervention dose in clinical trials (Sorkin et al. 2020) as promising preclinical NP research is not consistently translated into actionable clinical trial. Additionally, it is imperative to establish the dose-response curve and assess a spectrum of concentrations, ideally through in vitro studies as in vitro studies has the potential to predict in vivo response (Barnard & Gurevich 2005; Monika et al. 2022). Dose conversion from animal studies to clinical trial can be achieved through either allometric or mechanistic modelling approaches (Nair & Jacob 2016; Sharma & McNeill 2009).

Intraperitoneal injection is an

invasive method and rarely employed for treating cutaneous wounds in humans. It is primarily reserved for addressing peritoneal cancer and necessitates trained personnel for its administration (Al Shoyaib et al. 2020). During in vivo testing, the development of a drug formulation viable for promoting cutaneous wound healing is crucial, as subsequent clinical trial are likely to adopt a similar formulation (Sorkin et al. 2020). CAPE-based local wound dressings, such as hydrogels, present a promising option for this purpose. Hydrogels create an optimal microenvironment in the injured area, potentially enhancing the wound healing process (Stan et al. 2021). Moreover, certain transparent hydrogels facilitate easy clinical assessment of wound healing progression. Additionally, hydrogels enable the controlled and gradual release of bioactive components to the injured area at a specified rate over a defined duration (Francesko et al. 2018).

Interpreting data from animal studies should be done cautiously as animals differ from humans in several areas including genetic, surface area and lifespan (Sorkin et al. 2020). One of the approaches to improve predictive validity of animal models is by employing transgenic mouse (Fang & Mustoe 2008). Furthermore, transgenic mouse is a valuable model to identify the underlying factors and fundamental molecular pathway that explicitly elucidates the target of a product (Kim et al. 2001; Kitano et al. 2017). Alternatively, methods such as RNA interference can be employed

to reduce the expression of the target gene, enabling the observation of the outcomes associated with the inhibition of the pathway (Agrawal et al. 2003). Double-transgenic mouse and fluorescence imaging enhance the accuracy of measuring wound healing (Hu et al. 2018).

Although all the animal models in the papers presented were rodents, but they were different in genus and sex. This heterogeneity of the study design did not allow meta-analysis to be conducted. Conversely, heterogeneity in the animal models may offer information on the therapeutic response to a given product, distinguishing between responders and non-responders (Sorkin et al. 2020).

## CONCLUSION

This systematic review offers evidence supporting the effectiveness of CAPE in skin wound treatment, highlighting its antioxidant and anti-inflammatory properties. CAPE expedites wound healing by advancing the inflammatory phase, thereby accelerating the healing process, and effectively scavenging free radicals. With both its antioxidant and anti-inflammatory properties, CAPE serves as potential alternatives to current pharmacological treatment of various skin injury, including pressure ulcer, burn injury and incisional wound. Prior to evaluating the potential of CAPE in promoting wound healing in human studies, we recommend prioritising the investigation of its effectiveness through topical application, preferably utilising hydrogel wound dressings. Furthermore, refining drug formulation

parameters, including the intended dosage and administration route, is essential, as the findings from animal studies are likely to be utilised in clinical trials. Transgenic mouse is a valuable tool for gaining a deeper understanding of how a product elicits signalling in the body, contributing to the healing process.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interests regarding publication of this paper.

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